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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/943,054	08/30/2001	Seiichi Araki	0291266.00124US1	8743

23483 7590 10/21/2008

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EXAMINER
ANDERSON, JAMES D

ART UNIT	PAPER NUMBER
1614	

NOTIFICATION DATE	DELIVERY MODE
10/21/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	09/943,054	ARAKI ET AL.	
	Examiner	Art Unit	
	JAMES D. ANDERSON	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 March 2008 and 20 June 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3-6,8,9 and 58* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-6,8,9 and 58* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Copy of PTO/SB/51 (10-05)*.

DETAILED ACTION

Formal Matters

Applicants' response, filed 6/20/2008, is acknowledged and entered. Claims 1, 3-6, 8-9, and 58 are pending and under examination.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:

The foreign priority data required to establish a proper claim to a prior-filed foreign application is missing from the oath/declaration. In the previous Office Action, form PTO/SB/51 (10-05), which contains all of the required information, was attached for Applicant's convenience. Note the checkbox for claiming foreign priority under 35 U.S.C. 119. While applicants do not have to use the previously attached forms, a new oath or declaration must have all the information in the PTO-SB-51 (10-05) form. Another copy of PTO/SB/51 (10-05) with the required missing information highlighted is attached hereto.

Applicant's Supplemental Oath/Declaration filed 3/14/2008 is acknowledged but fails to correct the above identified deficiencies of the previous Oath/Declaration filed 1/9/2008. Applicant is further reminded that a Supplemental Reissue Oath/Declaration (as defined in the MPEP) cannot be based on a original Oath/Declaration that is defective, as is the case here. Accordingly, a new Oath/Declaration, not a Supplemental Oath/Declaration, is required to fix the above deficiencies of the original Oath/Declaration.

Claim Rejections - 35 USC § 251

Claims 1, 3-6, 8-9 and 58 are rejected as being based upon a defective reissue Oath/Declaration under 35 U.S.C. § 251 as set forth above. See 37 CFR § 1.175.

Claim Rejections - 35 USC § 112 – 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The rejection of claims 1, 3-6, 8, and 58 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, is **withdrawn** in light of Applicant's amendments.

Claim Rejections - 35 USC § 102 – New Grounds of Rejection

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Upon further consideration of the scope of the claims, which are given their broadest reasonable interpretation in light of the specification, the Examiner is herein reinstituting the prior art grounds of rejection made in the Office Action mailed 12/26/2006. Applicants amended the claims in their response filed 6/1/2007 to recite the limitation "....enhancing the immune response to infection by E. coli in a mammal in need thereof....", which the Examiner narrowly interpreted to mean that the mammal had an E. coli infection. However, upon further consideration, the claims are reasonably interpreted to encompass administration of the claimed active agents to any mammal. The claimed enhancement of immune response would be a natural result of such administration.

Claims 1, 4 and 5 are rejected under 35 U.S.C. § 102(b) as being anticipated by **Wertman and Sypherd** (J. Immunol., 1960, vol. 85, pages 511-515).

The instant claims are drawn to "....enhancing the immune response to infection by E. coli in a mammal in need thereof...." comprising administering riboflavin, flavin mononucleotide, flavin adenine dinucleotide, or pharmacologically permissible salts of riboflavin. Dependent claims 4 and 5 recite specific doses and administration routes, respectively.

Wertman and Sypherd evaluated the effects of riboflavin deficiency on rat susceptibility to infection with *Diplococcus pneumoniae* (Table III). *Ad libitum* rats were fed a basal diet *ad libitum* with a vitamin supplement containing 60 μg riboflavin (page 512). Rats initially weighed 34-35 g (Table I). Thus, the dose of riboflavin administered falls in the instantly claimed range (*i.e.* 1.7 mg/kg). Inanition control rats received only enough basal diet to maintain their weights equal to those of the riboflavin deficient animals (*id.*). Deficient animals received the basal diet ad libitum without a vitamin supplement (*id.*). At the end of 7 weeks, rats were challenged with virulent *D. pneumonie* (page 513). 83.3% of riboflavin deficient rats died compared to only 33.3% inanition rats and 0.0% *ad libitum* control rats (Table III). Riboflavin deficient rats fed 60 mg of riboflavin daily for 1 week following the 7-week riboflavin deficient diet and subsequently challenged with *D. pneumonie* only showed 9.1% fatality. Administration of riboflavin would be expected to naturally enhance the immune response to infection by E. coli in the riboflavin treated rats as recited in the instant claims. With respect administration of the coenzyme flavin mononucleotide or flavin dinucleotide, the reference inherently teaches this limitation because administration of riboflavin will naturally result in the production of these two coenzymes, as riboflavin is enzymatically converted to flavin mononucleotide, which then forms flavin dinucleotide.

The reference thus teaches that administration of riboflavin, in the doses and administration routes instantly claimed, protects rats from dying from an infection of *D. pneumonie* which inherently would result in enhancement of the immune response to infection by E. coli in the riboflavin treated rats as recited in the instant claims.

Claims 1 and 5 are rejected under 35 U.S.C. § 102(b) as being anticipated by **Ajayi *et al.*** (Eur. J. Haematol., 1990, vol. 44, pages 209-212).

The instant claims are drawn to "....enhancing the immune response to infection by E. coli in a mammal in need thereof...." comprising administering riboflavin, flavin mononucleotide, flavin adenine dinucleotide, or pharmacologically permissible salts of riboflavin. Dependent claim 4 5 recites specific administration routes.

Ajayi *et al*. administered riboflavin (5 mg) as a dietary supplement to 27 young Nigerian adults. Vitamin supplementation produced a significant hematological response, including increased hemoglobin concentration, hemocrit level and erythrocyte count (Abstract). The authors conclude that, even in malarial infection, hemoglobin concentration, hemocrit level and erythrocyte count were maintained if high vitamin (*i.e.* riboflavin) status was established throughout supplementation. Erythropoiesis is reported to be impaired in infection, and malaria parasitaemia alters hematological status (page 211). In the present study, successful control of malaria was not achieved with pyrimethamine, but high riboflavin status helped to maintain hemoglobin concentration and red blood cell count during malarial infection (*id.*). Administration of riboflavin would be expected to naturally enhance the immune response to infection by E. coli in the riboflavin treated rats as recited in the instant claims. With respect administration of the coenzyme flavin mononucleotide or flavin dinucleotide, the reference inherently teaches this limitation because administration of riboflavin will naturally result in the production of these two coenzymes, as riboflavin is enzymatically converted to flavin mononucleotide, which then forms flavin dinucleotide.

The reference thus teaches that administration of riboflavin, by the administration routes instantly claimed, which inherently would result in enhancement of the immune response to infection by E. coli in the riboflavin treated rats as recited in the instant claims.

Claims 1, 3, 5, and 9 are rejected under 35 U.S.C. § 102(b) as being anticipated by **Tsyganenko** (Vopr. Med. Khim., 1971, vol. 17, pages 364-369).

The instant claims are drawn to "....enhancing the immune response to infection by E. coli in a mammal in need thereof...." comprising administering riboflavin, flavin mononucleotide, flavin adenine dinucleotide, or pharmacologically permissible salts of

riboflavin. Dependent claim 3 recites further administration of an antibiotic effective against E. coli.

Tsyganenko teach that *Staphylococcal* necrotic infections decrease the activity of mitochondrial monoamine oxidase (MAO) (Abstract). Infected animals treated with the antibiotic, tetracycline, exhibited further inhibition of staphylotoxin-repressed MAO activity (*id.*). Treatment of animals with tetracycline in combination with vitamins B_2 and B_{12} ensured a restoration of MAO activity, repressed by antibiotics, to the level of non-treated animals (*id.*). The best stimulatory activity was observed with the combination of penicillin and vitamin B_2. In this case, MAO activity was higher in rabbits receiving antibiotics only and was restored to the level of enzyme activity in intact animals (*id.*). With respect administration of the coenzyme flavin mononucleotide or flavin dinucleotide, the reference inherently teaches this limitation because administration of riboflavin will naturally result in the production of these two coenzymes, as riboflavin is enzymatically converted to flavin mononucleotide, which then forms flavin dinucleotide.

Thus, the reference teaches administration of riboflavin in combination with an antibiotic to animals with an infection (*Staphyloccal* necrotic infection), which inherently would result in enhancement of the immune response to infection by E. coli in the riboflavin treated rats as recited in the instant claims.

Claims 1, 4 and 5 are rejected under 35 U.S.C. § 102(b) as being anticipated by **Zoltowska *et al***. (Wiad Parazytol., 1991, vol. 37, pages 247-253).

The instant claims are drawn to "....enhancing the immune response to infection by E. coli in a mammal in need thereof...." comprising administering riboflavin, flavin mononucleotide, flavin adenine dinucleotide, or pharmacologically permissible salts of riboflavin.

Zoltowska *et al*. administered vitamin B_2 (1 mg) to guinea pigs and on the 9^{th} day, post vitamin administration, the guinea pigs were infected with 5000 invasive eggs of *Ascaris suum* (Abstract).[1] The invasion lasted 6 days and was monitored by lung and

[1] *Ascaris suum* is a large roundworm parasite found in pigs.

kidney weight as well as the number of larvae in the lungs (*id.*). With respect administration of the coenzyme flavin mononucleotide or flavin dinucleotide, the reference inherently teaches this limitation because administration of riboflavin will naturally result in the production of these two coenzymes, as riboflavin is enzymatically converted to flavin mononucleotide, which then forms flavin dinucleotide.

Thus, the reference teaches administration of riboflavin to animals prior to infection with *Ascaris suum*, which inherently would result in enhancement of the immune response to infection by E. coli in the riboflavin treated mammals as recited in the instant claims.

Claims 1, 4 and 5 are rejected under 35 U.S.C. § 102(b) as being anticipated by **Folkers *et al***. (Proc. Natl. Acad. Sci. USA, 1984, vol. 81, pages 7076-7078).

The instant claims are drawn to "....enhancing the immune response to infection by E. coli in a mammal in need thereof...." comprising administering riboflavin, flavin mononucleotide, flavin adenine dinucleotide, or pharmacologically permissible salts of riboflavin

Folkers *et al*. orally administered 50 mg/day riboflavin to patients with carpal tunnel syndrome. With respect administration of the coenzyme flavin mononucleotide or flavin dinucleotide, the reference inherently teaches this limitation because administration of riboflavin will naturally result in the production of these two coenzymes, as riboflavin is enzymatically converted to flavin mononucleotide, which then forms flavin dinucleotide.

Thus, the reference teaches administration of riboflavin to those who had no prior infection, which inherently would result in enhancement of the immune response to infection by E. coli in the riboflavin treated subject as recited in the instant claims.

Claims 1, 4, 5, and 58 are rejected under 35 U.S.C. § 102(b) as being anticipated by **Mohammed *et al***. (USP No. 3,773,930; Issued Nov. 20, 1973) (newly cited).

The instant claims are drawn to "....enhancing the immune response to infection by E. coli in a mammal in need thereof...." comprising administering riboflavin, flavin

mononucleotide, flavin adenine dinucleotide, or pharmacologically permissible salts of riboflavin.

Mohammed *et al*. orally administered 100 mL of an aqueous composition comprising riboflavin, proline, and glutamine to rats (Examples 1-8). With respect administration of the coenzyme flavin mononucleotide or flavin dinucleotide, the reference inherently teaches this limitation because administration of riboflavin will naturally result in the production of these two coenzymes, as riboflavin is enzymatically converted to flavin mononucleotide, which then forms flavin dinucleotide.

Thus, the reference teaches administration of a composition comprising riboflavin, proline, and glutamine to rats, which inherently would result in enhancement of the immune response to infection by E. coli in the riboflavin treated mammals as recited in the instant claims.

Claims 1, 4-6, and 58 are rejected under 35 U.S.C. § 102(b) as being anticipated by **Wiuitz *et al***. (USP No. 3,697,287; Issued Oct. 10, 1972) (newly cited).

The instant claims are drawn to "....enhancing the immune response to infection by E. coli in a mammal in need thereof...." comprising administering riboflavin, flavin mononucleotide, flavin adenine dinucleotide, or pharmacologically permissible salts of riboflavin.

Wiuitz *et al*. teach compositions for administration to human comprising essential amino acids, essential mineral, and carbohydrates (Abstract). Such compositions can be formed as aqueous emulsions comprising the essential and non-essential amino acids, minerals, vitamins, carbohydrate and fat in balanced quantities (id.). An example diet formulation comprises the amino acids proline and glutamine as recited in claim 58 as well as the vitamin, riboflavin, as recited in claim 1 (Table I). A further example diet formulation comprises the amino acids proline and glutamine as recited in claim 58, the vitamin, riboflavin, as recited in claim 1, and polyoxyethylene sorbitan monooleate, which is a polyoxysorbitan fatty ester as recited in claim 6 (Table III). The diet formulations were administered in taste panel testing (Example VIII) With respect administration of the coenzyme flavin mononucleotide or flavin dinucleotide, the

reference inherently teaches this limitation because administration of riboflavin will naturally result in the production of these two coenzymes, as riboflavin is enzymatically converted to flavin mononucleotide, which then forms flavin dinucleotide.

Thus, the reference teaches administration of a composition comprising riboflavin, proline, glutamine, and polyoxyethylene sorbitan monooleate to humans, which inherently would result in enhancement of the immune response to infection by E. coli in the riboflavin treated mammals as recited in the instant claims.

With respect to the above rejections, it is noted that *In re Best* (195 USPQ 430) and *In re Fitzgerald* (205 USPQ 594) discuss the support of rejections wherein the prior art discloses subject matter, which there is reason to believe inherently includes functions that are newly cited, or is identical to a product instantly claimed. In such a situation the burden is shifted to the applicants to "prove that subject matter to be shown in the prior art does not possess the characteristic relied on" (205 USPQ 594, second column, first full paragraph). There is no requirement that a person of ordinary skill in the art would have recognized the inherent disclosure at the time of invention, but only that the subject matter is in fact inherent in the prior art reference. *Schering Corp. v. Geneva Pharm. Inc.*, 339 F.3d 1373, 1377, 67 USPQ2d 1664, 1668 (Fed. Cir. 2003); see also *Toro Co. v. Deere & Co.*, 355 F.3d 1313, 1320, 69 USPQ2d 1584, 1590 (Fed. Cir. 2004) ("[T]he fact that a characteristic is a necessary feature or result of a prior-art embodiment (that is itself sufficiently described and enabled) is enough for inherent anticipation, even if that fact was unknown at the time of the prior invention").

Though the cited references to not expressly teach "....enhancing the immune response to infection by E. coli in a mammal in need thereof...." (claim 1) as a result of the administration of the disclosed compositions to the subject, the administration of the compositions comprising the same compound(s) as claimed (e.g., those identical to Applicant's claimed compositions) to the same host (i.e., a mammal) as claimed is considered to necessarily have the claimed effect of enhancing the immune response to infection by E. coli, on the subject being treated, whether expressly recognized by the cited prior art or not. Products of identical chemical composition cannot exert mutually

exclusive properties when administered under the same circumstances or, in the present case, the same host. Please reference MPEP §2112.

In this case, the claims, in their broadest reasonable interpretation, do not require that the subject being administered the claimed compositions *is infected* by E. coli. For example, in Applicant's working examples, the claimed compositions were administered *prior* to inoculation of the subject with E. coli (see Examples at columns 5-8). Accordingly, the claims read on administration of a composition comprising riboflavin to any mammal.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James D Anderson/
Examiner, Art Unit 1614